Target Cell Limitation Model Derived with *in vitro* Data to Understand Viral Co-infection

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Abstract

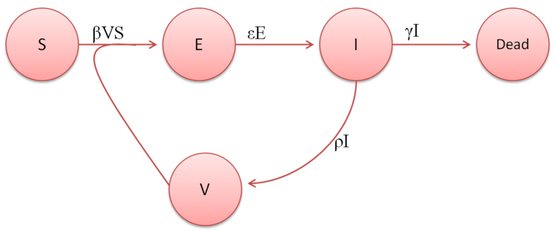
Two or more viruses are frequently detected in patients with severe respiratory tract infections. However, it is not clear how unrelated respiratory viruses interact within a host to alter disease severity compared to single virus infections. We are developing a mathematical model with *in vitro* data to study the effects of viral co-infection on shared target cells. A murine lung epithelial cell line was used to generate viral growth curves using rhinovirus (RV1B) and influenza A virus (PR8). These data were used to generate a target cell limitation model of viral growth during single virus infection. *In vitro* experiments are being done to expand the model to include rates of target cell growth and death, and viral decay. The model will also be expanded to include viral co-infection, including the growth rates of each virus and the rates of infection and co-infection of individual cells. The results of these studies will provide insight into the interactions between unrelated respiratory viruses during co-infection of shared host cells and organisms. This will provide critical insight into the pathogenesis of respiratory viral co-infections.

Model Basics

$$dS/dt = -\beta*V*S$$
$$dE/dt = \beta*V*S - \varepsilon*E$$
$$dI/dt = \varepsilon*E - \gamma*I$$
$$dV/dt = \rho*I$$

S = Susceptible cells
E = Eclipse-phase cells/ infected, no virus production
I = Infected cells, producing virus
V = Virus

β = Rate susceptible cells are infected
ε = length of time of the eclipse
γ = Death rate of infected cells
ρ = Rate of virus production from infected cells
E_o = Initial infected cells



Results

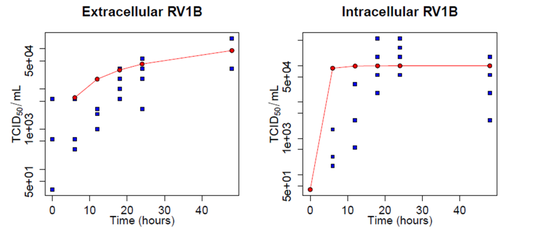
RV1B

- Extracellular virus increases over time likely due to virus being released from inside the cell
- Intracellular virus increases then stays the same due to reaching a threshold of virus contained in the cells. The actual data also shows a decrease, but that has not yet been put into the model
- The model represents the way this virus acts, which is to lyse a cell and leave no more virus in the cell

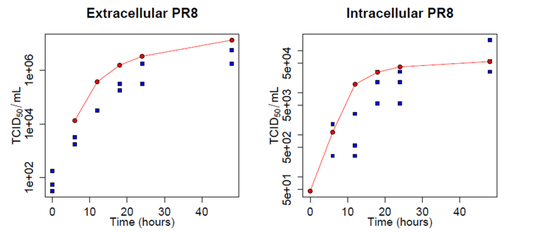
PR8

- Extracellular virus increases over time, likely due to virus being released from inside the cell
- Intracellular virus increases over time without slowing or decreasing
- The way this virus acts is also reflected in the model. PR8 is a budding virus, so virus is slowly released into the extracellular fluid while still keeping virus in the cell

Fitting the Model



β	ε	γ	ρ	E_o
7.6×10^{-1}	3.6×10^{-1}	5.2×10^{-6}	2×10^{-2}	3.9×10^{1}

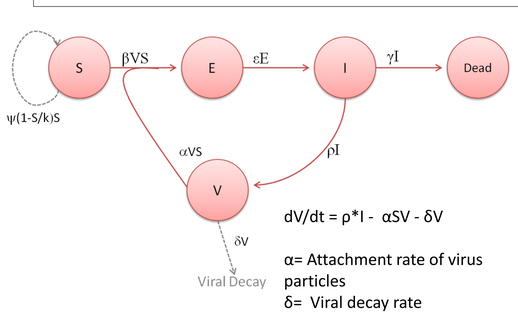


β	ε	γ	ρ	E_o
1.3×10^{-5}	3.8×10^{-2}	1.4×10^{-2}	8.2×10^{0}	4.6×10^{1}

■ = Data point collected in vitro
● = Model generated values
Tables represent values generated by model to fit data

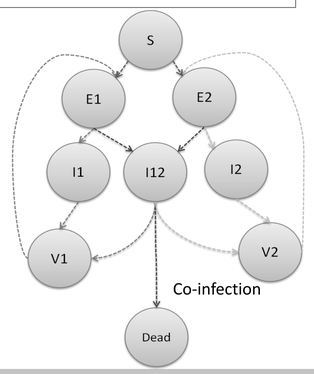
Expanding the Model

- Cell growth rate
- Counting cells → Calculate natural cell death
- Counting infected cells → Find how virus effects cell growth
- Viral decay rate → To know how much virus is made and lost in system
- Growth curve → $TCID_{50}$ to calculate viral titer
- Immunofluorescence assay → Counting single, co and non infected cells

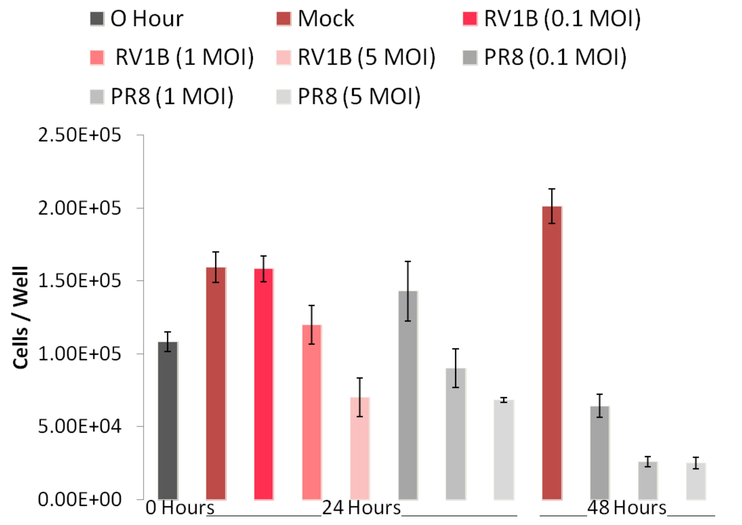


$dV/dt = \rho*I - \alpha SV - \delta V$

α= Attachment rate of virus particles
δ= Viral decay rate



Cell Counts



Cell Infection Rate

Figure 1. RV1B

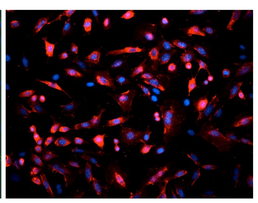


Figure 2. PR8

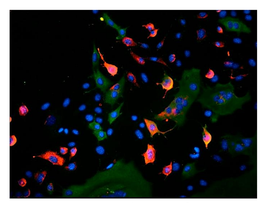


Figure 3. Example co-infection PR8 and MHV

- Green antibody stain detects RV1B
- Red antibody stain detects PR8
- Blue stain detects DNA and shows nuclei

- Green antibody stain detects MHV
- Red antibody stain detects PR8
- Blue stain detects DNA and shows nuclei

Generated Data Gives Insight on Co-infection

The model first takes single infection into consideration to show how a virus progresses on its own.

The next step of modeling will be to combine single infection models in a way that represents co-infection.

Having the ability to determine viral replication may help to understand the relationship between viral titer and disease severity. The data generated with this model can be used to compare with symptoms in disease severity.

Having a model will allow data to be generated at a faster rate to understand what is happening sooner.

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